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RESISTANCE AND DISEASE. PROBLEMS OF GENERAL PATHOLOGY

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16. Abstract

Resistance to disease is presented from the pathological viewpoint of the organism's reaction mechanisms, their regulation, stimulation, effect, reduced effectiveness and resultant change of effect. The role of stress is emphasized. General functional disturbances are dealt with in characterizing basic features of resistance and protection.

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I. RESISTANCE AND DISEASE. PROBLEMS OF GENERAL PATHOLOGY.

P. D. Gorizontov

Various pathological processes arise as a function of the specific nature of the action of certain etiological factors on the organism. There may be specific characteristics caused by the distinctive action of the stimulus. The present chapter provides only the characteristics of general features; this is completely justifiable, inasmuch as there are no processes which are characteristic only of extreme states of the organism. /7*

The problem we face is very extensive, and so we shall limit ourselves to those problems which are related to nonspecific resistance. These include mechanisms of integration and adaptation, since they are closely linked to the general resistance of the organism. This chapter will take up several problems of functional disturbances which are common to many diseases of the organism. The material is presented only on the "grand scale", but it still requires an introductory chapter which deals with several problems of general pathology in a pathophysiological fashion.

Principal Pathways of Injury; the Role of the Nervous System

The problem of pathological physiology does not involve listing the morphological changes that arise in various injuries. However, a functional analysis of the pathological processes cannot be carried out without regard to the structure and location of the injuries. We know that the cell is the basic structural unit of the organism, and damage to the cells is therefore a critical factor in the development of both altered functions and morphological disturbances.

Damage to the cells (and consequently the tissues) may occur in various ways. The pathogenic factor has either a direct harmful effect on the cells, or changes arise indirectly in the latter, i.e., through some agent. In the

*Numbers in the margin indicate pagination in the foreign text.

latter case, we can speak of the harmful influence on the cell of disturbances of nervous or hormonal regulation. Disruption of the vital activity of cells may arise as a consequence of intoxication or disruption of the internal environment of the organism, in other words, disruption of the homeostasis of the /8 medium in which the cells are living. Of course, it is possible that successive or joint involvement of various pathways could be involved.

Since the time of Claude Bernard, the term "homeostasis" has usually been interpreted to mean constancy of the internal environment of the organism. However, on the basis of the teachings of I. P. Pavlov, the phenomenon of homeostasis has acquired broader significance. In the first place, it governs the homogeneity of the internal medium; secondly, it governs the constant balance of the functions of the organism in accordance with the action of various factors on its external and internal environment. This does not mean a constant, but rather an uninterrupted, variation of certain properties and characteristics of the organism (naturally, within the limits of the variations considered standard). The variations can change within certain limits as a function of the action of environmental factors.

The vital activity of all of the cells in the organism takes place on the basis of phenomena of autoregulation, characteristic of all living structures. In a complex organism, the processes of cellular autoregulation do not occur independently. Cellular automatism is subject to the influence of regulatory systems which ensure higher integrative functions in the interests of the intact organism. The systems of general regulation include nervous and neuroendocrine systems. They exert their influence not only through nerve connections but also via humoral pathways. Important roles are played in these processes by the cardiovascular system, which ensures the circulation of fluid media through the organism (blood and lymph), as well as the organs of respiration and the liver and kidneys. However, the nervous system is critical to the regulation of the structure and function of the organism. To use the language of I. P. Pavlov, it controls the activity of all parts of the organism, beginning with the cell and ending with the organs and systems. The ideas of nervism in pathology, based on the work of Pavlov, have been covered by us in a special monograph, so that the role of the nervous system in this chapter will be discussed very briefly and schematically (P. D. Gorizontov, 1952).

With the participation of the nervous system, the most highly developed processes of adaptation are possible, even to abrupt changes in the environment. The nervous system plays an important role in compensatory processes. In this case, insufficiency of the function of any organ may be eliminated by increasing the activity of another organ and even various systems of the organism. It is important to keep in mind this respect that the phenomena of adaptation and compensation occur against the background of constant variation of the functions and structures of the corresponding cells, which we shall discuss in somewhat more detail below.

On the basis of the above, it is easy to see that in the case of various unfavorable life situations, and especially under the influence of extreme factors, the physiological stress on the nervous system increases sharply. Suffice it to say that all damage increases the flow of afferent impulsation from the focus of the injury to the central nervous system. This can cause disruption of nervous regulation of the functions, development of nervous dystrophies, and involvement of the nerve component in various pathological processes (A. D. Speranskiy). No considerable stress can be applied to the nervous system without consequences. Various phenomena involving weakening of the nervous system may arise from its overstimulation. Under such conditions, inhibition of the corresponding portions of the nervous system takes place. In serious cases, there is a profound and extensive inhibition in the form of coma, characterized by loss of consciousness and inability of analyzers to function.

The well-known studies of Pavlov and his school set down a number of the theoretically novel views that involve the biological significance of inhibition. /9
In particular, it was established that inhibition plays a limiting and limiting-remedial role (E. A. Asratyan, A. G. Ivanov-Smolenskiy).

The protective role of inhibition is dictated by the fact that sensitivity to the action of ordinary stimuli (normal sleep) or to the action of strong (extreme) stimuli (inhibition beyond a threshold) decreases or disappears. This protects the cells of the nervous system from further exhaustion.

The protective role consists in the fact that inhibition involves the nerve cells in processes of active recovery, accompanied for example by an increase in the accumulation of energetic material (ATP) and the elimination of the end products of metabolism. In this connection, under extreme influences, sedatives and soporifics are frequently prescribed when certain clinical symptoms are present.

While the processes of adaptation to constantly changing ordinary conditions in the environment take place quietly and unobtrusively, under the influence of unusually strong stimuli a profound stress is sometimes imposed on all of the forces of the organism. The stress is most likely accompanied by processes which promote the recovery of the vital activity not only of the nervous system but of other organs and tissues. Such a condition, or more exactly, a reaction, is called stress. At the present time, we have no data on the interreactions between the protective inhibition mechanism and the stress reaction.

Many of the problems associated with questions of recovery and exhaustion remain to be investigated.

Stress

This term is used extensively in modern literature on pathology. Literally translated, it means "imposed force". This concept has been used in medicine for a very long time, since even normal activity of an organism may be accompanied by an increase in the function of certain systems in the organism (stress on hearing, vision, muscular stress, etc.). As it applies to problems of pathology, the term "stress" was first used by Cannon. Then Selye developed a whole school of stress, according to which any disease constitutes a stress reaction. Theoretically, such a view is valid to a certain extent since there is a stress on the activity of the organism during illness and a number of reactions occur which are aimed at restoration of the equilibrium which has been disturbed. It has been known for a long time (and there is nothing surprising about it) that the ability of the organism to survive even temporarily under very unfavorable living conditions was developed through evolution. However, many of Selye's views are couched in overly simplified terms.

Selye concretizes his concept of stress by saying that it involves all of the nonspecific reactions of the organism that arise under the influence of pathogenic factors. However, this explanation is not very clarifying, since the division of the reactions of a sick organism into specific and nonspecific is a very arbitrary matter; it is metaphysical and based on concepts of formal logic.

In reality, there are no absolutely specific processes which are typical of only one disease. However, this does not mean that various diseases do not have their own qualitative characteristics. In any nonspecific reaction (for example, in inflammation, fever, reactions of the blood system, cardiovascular /10 system, etc.) there may be (particularly in a more profound study) characteristic features that are caused by the action of precisely that pathogenic stimulus. The specificity is determined by the considerable variability of the general (nonspecific) processes of pathology. Since the time of Virchow it has been known that reactions can change either in their intensity (heterometry), duration or time of development (heterochrony), or location (heterotopy). As a result, one can generally find the outlines of the partial (and therefore specific) and even a partial development of the general. This is the law of dialectics.

Thus, there are no specific or nonspecific reactions which exist separately. Hence, regardless of the views of Selye and his attempts to give the concept of "stress" a general expression for all nonspecific reactions in the form of an adaptational syndrome, the majority of researchers understand the stress reaction to be composed of processes associated with an increase in the activity of the secretion of ACTH by the adenohypophysis and the corticosteroids of the adrenal cortex. It should be mentioned that the role and mechanisms of the actions of these hormones in pathology have largely not yet been studied. The great contribution of Selye has been to discuss the problem of stress itself and the experimental development of this problem. His works established the role of hormonal phenomena in stress reactions. It was shown that an increase in the secretory activity of the hypophysis and the excretion of ACTH, and therefore an increase in the activity of the adrenal cortex and the excretion of the glucocorticoids, are important factors in the first stage of the stress reaction (the stage of fear or mobilization). The hormonal reaction that arises under the influence of the nervous system allows the organism to shift to the next stage – the stage of increased nonspecific resistance. Insufficiency of the adrenal cortex definitely causes a sharp decrease in the resistance of the organism. Within the resistance stage, recovery of the organism may occur. However, the next stage may also develop – exhaustion of the organism, characterized by weakening of the protective forces which may end in death. The reasons for the development of resistance and exhaustion in the organism are not clear.

Without characterizing the various periods of the stress reaction in detail, we can confirm that, generally speaking, the division of the changes in the state of the organism into periodic phases actually exists. It was repeatedly observed in both clinical and experimental pathology prior to and independently of the work of Selye. It is sufficient to refer to the classical studies of N. Ye. Vvedenskiy on parabiosis.

The work of Selye has shown that on the basis of a hormonal conditionality, i.e., excess content of gluco- or mineralocorticoids in the organism, especially in conjunction with the action of certain other stressors, development of various pathological processes may occur. A similar situation arises in disturbances of hormonal regulation of processes, caused by inadequate reactions of the adrenal cortex.

Pavlov and his school discovered the significance of the disturbances in the neurological status in the form of experimental neuroses as the basis of the development of diverse forms of pathology (M. K. Petrova, A. D. Speranskiy and others). This has been extensively confirmed, for example, in the cardiovascular disease clinic. The pathogenic action of various factors is sharply increased in animals with experimental neuroses.

Thus, it has been demonstrated experimentally that disruption of the regulatory role of both the nervous and hormonal systems may constitute a basis for pathology. Disturbances of regulation increased the sensitivity of the organism to the action of extreme stimuli and even determined the location of /11
the damage.

Following damage to an organism caused by an pathogenic factor, complex processes arise in which it is difficult to separate the "breakdown" from the "physiological measure" against the disease. This is because there is nearly always a shifting of the cause-result relationships. In a large organism, there is even a change in the role of unambiguous processes. For example, inflammation may have a protective role at one stage of a disease and may be very harmful at another (for example, limitation of the activity of an organ due to the formation of a scar or the toxic action of an exudate).

For example, by using a specific amount of electrical stimulation, as a function of the force and duration of the action of the electrical current, one can obtain a stress reaction of varying intensity and duration. Thus, with a pulse duration of approximately 2 seconds, a pulse interval of 1 minute, a current strength of 2 mA, a frequency of 2,000 Hz and daily stimulation lasting 6-8 hours, rats develop characteristic weight changes corresponding to the stages of the stress reaction.

The rats grew steadily, so that weight constituted a general index of the balance of catabolic and anabolic processes, changing as a function of the stages of the stress reaction (Figure 1). In such experiments, the condition of increased resistance was repeatedly checked relative to other pathogenic stimuli.

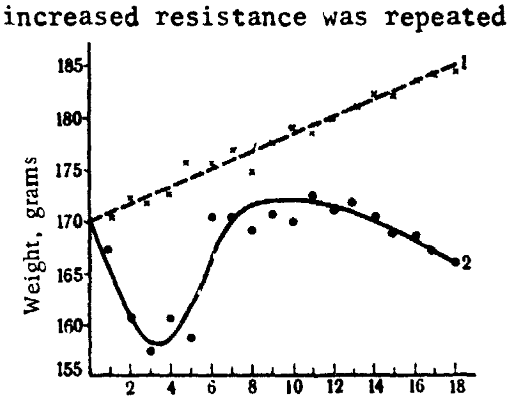


Figure 1. Change in the Weight of Rats With a Stress Reaction as a Function of Daily Electrical Stimulation. 1, Weight of control rats; 2, weight of experimental rats; 1st to 5th days, stage of mobilization; 6th to 12th days, stage of resistance; after the 13th day, stage of exhaustion.

On the basis of its biological significance, the stress reaction is essentially a reaction involving adaptation to extreme conditions. Under ordinary conditions, as we have already pointed out, the adaptation reaction occurs with involvement of the nervous system; under pathological conditions this participation is even more necessary. In fact, on the basis of work performed by L. A. Orbel', Cannon and others, it may be considered established that the increase in the tone of the sympathetic nervous system accompanying the secretion of adrenaline and the activation of the secretion of the hypothalamus is an initial, triggering mechanism for the stress reaction. The adaptational-trophic role of the sympathetic nervous system was demonstrated long ago. Corresponding examples will be given below. Under pathological conditions, there are no new mechanisms of resistance or adaptation that develop, so that there is nothing surprising in the fact that the sympathetic nervous system itself reacts primarily.

Hence, we understand the stress reaction to be the involvement in regulation of adaptational mechanisms of the following systems: hypothalamus → anterior lobe of the hypophysis → adrenal cortex → tissues and organs.

We can clarify the role of this system after a brief discussion of problems of resistance and mechanisms of adaptation.

Nonspecific Resistance of the Organism and Mechanisms of Adaptation /12

In his day, the famous American physiologist Cannon concluded that the organism of animals has a considerable "reserve strength"; it is not structured along the lines of a specific limit and the principle of the strictest form of economy. Numerous facts support the first view. For example, the normal maximum arterial pressure varies from 110-120 mm Hg. However, the pressure can fall to 70-80 mm Hg before a critical level is reached at which the blood supply to the tissues becomes insufficient. The heart can increase the number of its contractions by a factor of 2 at any time and the arterial pressure can rise 30-40%. The heart is the most adaptive organ, richly endowed with reserve capacity.

The function of respiration also has a considerable reserve strength: we know that life can continue when a great deal of the lung tissue has been damaged or removed. Moreover, arterial blood contains approximately 3.5 times more oxygen than is usually used by the tissues. One can remove the greater part of the stomach or about two-thirds of the small intestine or most of the large intestine without significant changes occurring. The organism can withstand removal of three-fourths of the liver and total extirpation of the spleen. Since the time of the studies of Richards, it has been known that a portion of the nephrons do not work constantly and constitute a reserve. Removal of two-thirds of each kidney can be performed without serious disrupti of kidney function. The volume and composition of the urine remain practically constant when this is done. Experiments have shown that one-tenth of the adrenal tissue is sufficient to support life, while total removal of both adrenals leads to rapid death of animals within maximum limits — up to 36 hours. Extirpation of four-fifths of the thyroid gland will not cause symptoms of myxedema. Removal of both parathyroid glands does not result in any changes in calcium metabolism. It is sufficient to have one-fifth of the tissue in the pancreas in order to meet the needs of the organism for insulin and to avoid symptoms of diabetes.

All of these facts indicate that the functions of many organs are several times greater than the needs of the organism for normal activity. However, this does not mean that the nature of living organisms is wasteful or uneconomic. In contract to machines and other technical equipment, the "reserve strength" in a living organism is achieved in various ways: here, there is an intensification of the function of a certain organ not only due to the reserve forces but also because of changes in metabolism, involvement of other systems in the organism, changes and structures, etc.

It may now be considered established that following removal of any part of an internal organ, replacement by hypertrophy of the corresponding tissue will occur. Hypertrophy, essentially speaking, is the regeneration of the organ in the morphological and functional sense. Hence, the "reserve strength" is governed by the potential plastic capacities which actually arise at quite remote periods following extirpation.

There are many facts which indicate that the path of evolution has been marked by an improvement in the most "economical and profitable" expenditure of energy and materials. Thus, for example, we know that the available amount of blood is many times less than the volume of the vascular bed, and the organism can meet its needs with a comparatively small amount of blood. The oxygen distributors, the erythrocytes, require a minimum amount of oxygen for their needs. Their disruption of the rinciple of economy can occur only under pathological conditions, when the retention of life in any form is the final step in the existence of the structural unit or the organism as a whole. /13

In addition to the "reserve strength" of various organs and systems, nonspecific resistance is assured by a number of other characteristics which make it possible for the organism to withstand various changes in the extern l and internal environment. These include in particular the intactness of the cutaneous coverings and the mucous membranes, which prevent the penetration of various harmful or foreign substances into the organism.

The protective reflexes, such as sneezing, coughing, etc., promote the removal of irritating agents from the respiratory organs. As the studies of Pavlov have shown, such harmful substances as acids or alkalis that enter the mouth or stomach can be rapidly diluted by saliva, gastric juice, etc., or expelled by spitting or vomiting — this is how the gastrointestinal tract and the organism as a whole are protected against harmful substances. The principle of duplication of organs unquestionably increases the probability of preservation of the corresponding functions (kidneys, lungs, adrenals, etc.). The principle of the duplication of functions operates similarly. For example, the splitting of proteins is accomplished by enzymes in the gastric juice and the pancreatic juice, while carbohydrates are split by enzymes i the saliva and pancreatic juice. Excretory processes are carried out by the kidneys and partially by the sweat glands.

The principle of the duplication of functions also involves the nervous system and the endocrine glands in protective reactions to a certain extent. Increasing the nonspecific resistance may also be the consequence of a change in activity, for example, of the sympathetic nervous system, and an increase in the secretory activity, for example the hypophysis and adrenal cortex. However, this is not a sufficient basis for concluding that the mechanisms of the influence of these systems on the resistance of the organism are identical and equivalent.

There is an entire system of cells in the organism whose role was first studied by I. I. Mechnikov, V. K. Vysokovich, A. A. Bogomol'ts and other authors. This is the so-called reticuloendothelial system, or the system of the active mesenchyma, which has a wide variety of functions related to the maintenance of the internal environment of the organism. In particular, the microbes which penetrate the organism are captured and destroyed by the cells of the reticuloendothelial system. The basic substance of connective tissue acts as the moderator of cell energy. The toxic effect various poisons depends upon the functional state of the cells of the reticuloendothelial system and the basic substance. When the functional activity of the reticuloendothelial system increases, toxicity may be reduced many times; on the other hand, when the activity of the reticuloendothelial system slackens, the consequences of poisoning may be considerably worse.

Special mention should be made of the fact that the liver has a detoxifying function which consists in the neutralization of poisonous substances by means of their combination with sulfuric or glucironic acid or the destruction of the toxins.

The systemic principle is particularly effective as far as ensuring the basic functions is concerned, which may be critical under certain conditions (when the organism is in an unfavorable state). Thus, for example, when there is a shortage of oxygen in the organism, there is not only a speeding up of the rhythm of respiratory movements but a simultaneous increase in the number of cardiac co ractions, the blood flow speeds up, there is a rise in arterial /14
pressure, redistribution of the blood supply, and introduction of erythrocytes into the general circulation through contraction of the spleen; these erythrocytes are retained in the spleen tissue as a reserve. In the final analysis, all of this is for one purpose — increasing the supply of oxygen to vitally important tissues.

However, activation of the principle of systemics cannot take place without higher integrative functions of the organism. In this respect, as we have already mentioned, an important role is played by the nervous system. The adaptational-trophic role of the sympathetic nervous system was established by L. A. Orbel' and Cannon.

Cannon points out that the sympathetic-adrenal system plays an important role in blood loss, speeding up the process of blood coagulation and causing the contraction of the peripheral vessels, thus promoting a retention of the blood in the organism. When the ambient temperature falls, the action of the sympathetic-adrenal system causes a narrowing of the peripheral vessels, elevation of hair or bristling of the fur due to the contraction of the pilomotor muscles. This leads to a reduction of heat loss. The secretion of adrenaline promotes an increase in the oxidative processes and a rise in heat production. Removal of the sympathetic nodes (thoracic, abdominal) in animals (cats) results in reduced resistance to the action of low temperatures: the pilomotor reflex is absent, the peripheral vessels do not constrict, and adrenaline is not secreted. As a result, after spending 2.5 hours in a room (for example) at a temperature of 0.8-6°, sympathectomized cats showed a drop in body temperature while control animals remained at normal levels. Sympathectomized monkeys showed reduced resistance to the action of high temperature. Monkeys suffered overheating in the sun and developed heat stroke. No disturbances of any kind were observed in normal monkeys under the same conditions.

By limiting ourselves to these examples, we can see that the sympathetic nervous system plays an important role in the adaptation of the organism. As we mentioned earlier, it is involved in the activation of the hormonal system of the hypophysis and adrenal cortex in the stress reaction. Clearly, the stress reaction must be viewed as an adaptation to more serious influences, requiring the activation of additional mechanisms for recovery and protection. However, the question of the specific mechanisms involved is still not sufficiently clear.

It may be considered established that the glucocorticoids support gluconeogenesis, working with adrenaline to promote the mobilization of sugar which improves the supply of the tissues with "fuel". The glucocorticoids have a stabilizing effect on the cell membranes. As will be shown later on, the disturbance of the cell membranes may play a critical role in the development of cellular pathology and in the deaths of cells. By causing the death of lymphoid cells, the glucocorticoids enrich the internal environment with antibodies and thereby increase the protective action of the medium. The lymphocytes, by being destroyed, carry out a trophocytic role: for example, the DNA of the lymphocytes may be utilized in processes of repair and regeneration of damage

to tissues. I. N. Kendysh and B. B. Moroz have shown that when lymphocytes are destroyed under the influence of hydrocortisone as a plastic material, in addition to the nucleic acids, amino acids and their metabolites are used. The increased contents of these substances may cause activation of glyconeogenesis and synthesis of protein in the liver. It has been established that the processes of activation proceed more rapidly under the influence of the lymphoid cells present in the medium. The corticosteroids have a significant influence on the intensity of the inflammatory reaction. Insufficiency of hormonal /15
function of the adrenal cortex causes a sharp drop in the resistance of the organism. We know that even an insignificant trauma in the presence of insufficient function of the adrenal cortex can lead to the death of the organism.

Regulation, Resistance and Adaptation on the Cellular Level

On the basis of the data presented above, it must not be concluded that the resistance and the adaptational mechanisms operate only on the level of organs or systems of the organism. Every cell has various mechanisms that ensure cellular resistance. These include: phagocytosis, cellular excretion, resynthesis of proteins and damaged structures. The effectiveness of these mechanisms is a function not only of the general but also of the local regulation of functions. The processes of local and general resistance are interrelated.

The cell, as an intact structure, has its own level of integration and regulation of functions. By integration, we mean here the coordinated action of all the cell structures. From this standpoint, the nucleus is the most important structure. The genetic apparatus of the nucleus exerts control over the processes of biosynthesis and over the reproduction of cell organelles. However, in addition to the genetic control factors, encoded in the DNA of the cell nucleus, there are cytoplasmatic integration factors, among which the most important role is played by the mitochondria (S. A. Neyfakh).

The mitochondria are the basic "energy factories" of the cell. It is here that the accumulation of energy takes place, in the form of compounds that belong to the adenyl system. Energy is generated as the result of a conversion of adenosinodiphosphoric acid (ADP) into adenosinotriphosphoric acid (ATP), rich in energy, through the phosphorylization reaction. The phosphorylization process, i.e., the joining of inorganic phosphorus ($P_{inorg.}$) takes place by virtue of the energy which is obtained from the oxidation of various substances (proteins, fats, carbohydrates) by means of oxidizing enzymes. The reaction in which ATP is formed has the following equation:

$$NAD = H_2 + 1/2\ O_2 + 3\ ADP + 3\ P_{inorg.} \rightarrow NAD + H_2) + 3\ ATP$$

(NAD is nicotinamide adenine dinucleotide, $NAD = H_2$ is reduced nicotinamide adenine dinucleotide). This process is reversible. Liberation of energy through the breakdown of ATP leads to the formation of ADP:

$$ATP + H_2O \rightarrow ADP + P_{inorg.}.$$

The energy given off by ATP when this substance breaks down is used to ensure the functioning of the cell and for various biosynthetic processes. The oxidation energy not only goes to synthesize ATP but to form heat as well.

The general mechanism of cellular automatism in the regulation of the functions of metabolism consists for example in the fact that the products of the breakdown stimulate the synthesis of the raw material. Thus, the ADP which is formed as a result of the breakdown of ATP stimulates the resynthesis of ATP and thereby ensures that the energy resources are kept at the original level, while an increase in the synthesis of ATP inhibits other processes in the cell).

It has been established (S. A. Neyfach) that mitochondria play the leading role in the changes in activity and in other organelles of the cell. It is clear therefore that the mitochondria are the most reactive structures in the cell. Their size changes rapidly under the influence of stressors of any kind. /16
However, as L. A. Orbel' pointed out in his day, in the course of evolution the older forms of cellular automatism have been suppressed by later forms of regulation involving the organism, in the form of nervous and hormonal control. The obvious nature of such relationships is beyond dispute, although the concrete mechanisms of this regulation remained undiscovered for a long time. In this respect, considerable interest attaches to the work of V. S. Il'in and his school, who showed that hormonal control (insulin, oxytosin, vasopressin) can

be achieved through changes in the permeability of cell membranes, activity of enzymes and the rate of synthesis of enzymes. Let us examine an example of permeability.

According to V. S. Il'in and T V. Titova, molecules of insulin and other hormones are fixed in the proteins or lipoproteid cell membranes through the bonding of their disulfide bonds (-S-S-) with the sulfhydril groups (-SH) of the protein receptors. This leads to the formation of hormone-protein complexes. The complexes change the conformation of the membrane proteins (or the lipoproteins) and thereby increase the permeability of the membranes.

The molecular mechanisms of the decrease in permeability of the cell membranes on the influence of glucocorticoids have not yet been completely explained.

The role of the nervous system in the regulation of the cell metabolism was demonstrated in the work of V. S. Il'in. Without going into a biochemical treatment of these studies, we will merely mention that in denervated tissues (liver, muscle) the synthesis and activity of the enzymes involved in the metabolism of glucose change in a fashion which causes the metabolism to resemble that in embryonal tissues. For example, following denervation, the reactivity of the cells in the liver to the injection of glucose was lost. In intact animals, the administration of glucose causes, for example, increased synthesis of glucokinase. This did not take place in the tissues of the denervated liver. Following various experiments and studies, Il'in concluded that the elimination of nerve connections largely decreases the adaptational capacities of tissue.

Thus, one of the mechanisms of adaptation of cells is an increase in the corresponding synthetic processes. How is this accomplished? The DNA of the nucleu which contains the entire code of genetic information, regulates the nature and intensity of the synthesis through RNA by virtue of a change in the amount of open (active) and closed (passive) parts of the DNA or the genes. If it is satisfied, the corresponding active parts of the DNA molecule are repressed. Increased demands for some substance cause an increase in the functional activity of the corresponding part of the DNA through the involvement of hormones, which cause depression of the necessary part of the DNA. The role of synthetic processes in pathological examples was demonstrated in the work of F. Z. Meyerson, who developed the idea of the plastic quaratee of functions. The author notes that any disturbance will ultimately lead to insufficient synthesis of nucleic acid. This will unavoidably affect the functional activity of the cells and their ability to recover. However, the damage to chromosomal DNA which occurs even under "normal" conditions of lide of a cell or under the influence of pathogenic factors may be repaired. At the present time, it has been demonstrated that the cell contains special enzyme systems that cause the splitting off of the damaged part of the damaged part of a molecule, cross-link, etc. It is possible that similar processes increase the resistance of the cell.

Increasing the activity of the mitochondria leads to an increase in the synthesis of macroergic compounds (ATP and others) which are vitally necessary in order to increase the vital activity of the cell. Under ordinary adaptation conditions, this is accomplished through oxidation phosphorylization. Under unfavor-ble stress conditions (for example, heavy work, hypoxia, etc.) ATP synthesis may occur outside the mitochondria through the inclusion of anaerobic glycolysis, a less economic process. Inclusion of anaerobic glycolysis is caused by a change in the structure and permeability of the cells in the membranes of the mitochondria. This allows penetration of the ATP and the enzyme kinazine into the cell, thus stimulating the development of aerobic glycolysis in the cytoplasm. /17

The cell organelles sometimes perform similar functions. According to Neyfakh, the genetic information of at least some proteins is encoded in the DNA of the mitochondria. Thus, adaptation of certain synthetic processes may be regulated by the mitochondria themselves without the direct influence of DNA from the nucleus of the cell. This indicates that the principle of duplicating the functions is carried out to some extent on the cellular level as well. Duplication of functions by various organelles unquestionably increases the resistance and adaptational capacities of the cell.

Oxidative processes are related to adaptation to the action of low temperatures. Under optimum conditions, as we pointed out earlier, oxidation and phosphorylization are related processes, whose intensity is expressed by the coefficient P/O. The coefficient can be decreased by generalization of the phosphorylization and oxidation processes. Generalization is caused by large doses of thyroxin, certain substances (dinitrophenol, phenyl hydrazine, amytal, etc.), and a decrease in temperature. Let us recall that oxidation is a source of heat. V. P. Skulachev established that cooling of animals causes a drop in P/O in muscles but no change in the liver. The decrease in P/O in the muscle tissue had a pronounced adaptive nature and influenced the general condition of the animals, particularly with repeated cooling. The following table was taken from a monograph by V. P. Skulachev (Table 1).

TABLE 1. EFFECT OF COOLING ON P/O VALUE IN THE MITOCHONDRIA OF THE LIVER AND MUSCLE OF THE PIGEON

Treatment of the pigeon	P/O	
	Liver	Muscle
Without cooling	1,40±0,11 (10)	0,85±0,10 (13)
After repeated cooling	1,40±0,08 (9)	0,15±0,05 (8)

Note: The numbers in parentheses indicate the number of animals. Commas indicate decimal points.

The low P/O coefficient of the muscle mitochondria made it possible to maintain temperature despite the intensive heat loss. Animals which retained a high P/O in the muscle mitochondria, and thus a conjugation of oxidation and phosphorylization, rapidly entered hypothermia and died. Substances which increase generalization or cold training increased the survival of the animals. This may be viewed as an example of the interaction of the adaptation process /18
on the cellular level and in the organism as a whole.

According to Skulachev, adaptation of animals to a sharp drop in temperature occurs in three stages (Figure 2). The first stage is characterized by hypothermia and temporary stimulation of gas exchange, replaced by slow breathing; this is followed by a relatively slight generalization of oxidation and phosphorylization in the muscles. In the second stage, there is a further separation of respiration and phosphorylization in the muscles; the body temperature and gas exchange stabilize. The third stage is accompanied by a decrease in separation of respiration and phosphorylization and stimulation of gas exchange, as well as an increase in body temperature.

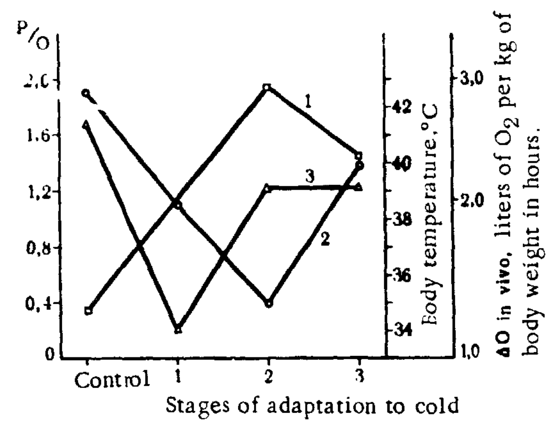


Figure 2. Stages of Adaptation To Cold in the Pigeon. 1, Oxygen consumption; 2, P/O in the mitochondria of the pectoral muscle; 3, body temperature.

Finally, a very important mechanism which determines the resistance of previously damaged tissue is the process of cellular repair and recovery. It is usually related to an increase in the mitotic activity of the cells. Here the most important role is played by the matrix synthesis of the DNA molecules. Cell division is accomplished through a rise in the activity not only of the nuclear function but of the cell as a whole. A change in mitosis cannot be viewed solely from the standpoint of local effects. To determine the role of the organism, numerous facts can be presented which indicate that the intensity of the mitotic processes is a function of the general state of the organism, the influence of nervous and hormonal systems, etc. (I. A. Alov).

The experiments of V. P. Pashchenko demonstrated that a single cooling of the organism causes a change in the state of the cells of the kidney which is characterized by the fact that a culture of kidney tissue from such animals showed a reliable increase in the number of cells. In prolonged unfavorable exposure (starvation) the author observed inhibition of cell growth in tissue cultures. Loran and Carbone, in experiments performed in rats with parabiosis, found that resection of 10% of the small intestine was followed by the appearance of substances in the blood which stimulated the mitotic activity and the processes of proliferation of the intestinal epithelium in the unoperated animals.

However, in the examples cited above, the role of the organism is far from clear; the significance of the sympathetic nervous system and the corticosteroids has not been determined; the influence of various stages of the adaptational syndrome has not been determined.

Damage to Cells

Pathology has long been familiar with degenerative changes in the cell in the form of turbid swelling, vacuolization, hydropic degeneration, infiltration by various substances, etc. These terms do not fully reveal the nature of the changes. The functional characteristics of the damaged cells are really only beginning to be studied. Successes have been achieved through use of methods of /19
electron microscopy and molecular pathology.

Special studies performed by Trump and Ginn (1969) revealed that various interventions influencing protein metabolism and protein synthesis do not themselves cause the death of the cell. In this respect, the cells were most sensitive to hypoxia. Oxygen starvation causes insufficiency of energy formation, which is very dangerous to the life of the cell. However, the last step in any kind of damage to a nondividing cell consists in the destruction of the permeability of the cell membranes.

Destruction of cell membranes may be primary or secondary; the latter can occur, for example, in hypoxia, and insufficient ATP formation. Regardless of the method of damage to the plasmatic envelope, disturbance of the internal medium of the cell occurs. This is accompanied primarily by a loss of potassium and increased penetration of sodium and water into the cell. It must be taken into account that all the structures of the cell have membranes with different structures and permeabilities having different functional significance. Therefore, when the permeability of the cell membranes is destroyed, there is an inhomogeneous swelling of the intracellular structures, disruption of their functions and if the processes are irreversible -- death of the cell.

Modern pathology cannot be satisfied with a simple confirmation of damage to cells or their deaths. Disturbance of the functional activity of a cell or its death may largely depend on which functional structures (organelles) were damaged.

The nucleus of the cell is the most important structural unit. Without the nucleus, life would be nearly impossible for cells. An exception is the mature erythrocyte, which is incapable of dividing, however. Damage to the cell nucleus is accompanied by genetic disturbances or loss of the ability spontaneously to produce cell substance in dividing cells. Damage to the nucleus in cells during the interphase period causes a number of functional disturbances.

On the basis of data on the role of the basic subcellular structures, we can represent schematically the most important consequences of damage to them. For the sake of brevity, we have presented these points in Table 2; the specific characteristics of intrinsic functions of the various organs were not taken into account.

As we can see from Table 2, the mitochondria obviously react to any kind of change. In his survey article, A. G. Bulychev describes the lability of the mitochondria and the high degree of dynamicity, using the term "dynamicity" to represent the change in various structural elements of the mitochondria and their rapid recovery. This finding is based on numerous studies by a number of authors, who showed that disturbance of the functions of the mitochondria occurs during starvation, the action of various physical and chemical factors, under the influence of hormones, vitamin deficiency, etc. For example, in mechanical traumas the mitochondria swell and become "coarser". Poisoning by phosphorus causes agglutination of the mitochondria; they dissolve and change into fatty inclusions. There are frequent cases in which the mitochondrial membranes are broken: fragmentation of the crypts and other changes of a destructive nature occur. It should be pointed out that small doses of thyroidin hormone cause an increase in the number and size of mitochondria.

The mitochondria are particularly sensitive to a decrease in the concentration of oxygen. According to the data of Mora and Brody (cited in A. C. Bulychev, 1969), there is a separation of the oxidative phosphorylization and a drop in the K^+ level. Disturbances of metabolic processes, like morphological ones, are characterized by a high level of reversibility. However, the effect of extremal factors may be so great that insufficiency in supplying energy materials may be accompanied not only by suppression of functions but by death of the cell. An important role in resistance and damage to cells is played by the lysosomes, which constitute sites for the accumulation of enzymes that possess the ability to perform hydrolytic splitting of various substances. Bacteria and foreign substances that enter the cell are subjected to enzymatic destruction. In this way, the lysosomes ensure preservation of the internal medium of the cell. However, De Duve (cited in A. G. Bulychev, 1969) was the first to point out that ruptures of lysosomal envelopes have a fatal effect on the cell due to the escape of proteolytic lysosomal enzymes into the surrounding medium. In this way, the phenomena of autolysis develop, i.e., enzymatic self-destruction of tissue elements.

TABLE 2. BASIC FUNCTIONS AND CONSEQUENCES OF DAMAGE TO CERTAIN STRUCTURES OF THE CELL

Structure	Brief biochemical and functional characteristics	Particular sensitivity	Possible consequences
Nucleus	DNA, all types of RNA, histones and DNP, lipoproteins and other proteins. Basic functions: in cell division, processes of reproduction and regeneration, synthesis of nuclear DNA and proteins, in the control of synthesis of proteins and polypeptides in the cytoplasm through the formation of informational RNA.	To the action of ionizing radiation free radicals, alkylizing substances, purin analogs, etc.	Disruption of mitotic activity. Genetic death. Change in genetic properties. Change in the functional properties of the cell and the enzyme composition.
Nucleoli	High RNA content. Influence on synthesis of nucleoproteids, RNA of cells, activity of cytoplasmatic organelles influence on mitosis.		Disruption of nucleoproteid metabolism and cell division.
Endoplasmatic reticulum in the form of smooth structures for ribosomes (ergastoplasm)	RNA from nucleus and nucleoli, containing genetic code for synthesis of protein synthesis of enzymes Metabolism of carbohydrates, fatty acids, steroids (cholesterol). In the liver — detoxic function.	To the insufficiency of energy resources	Disruption of metabolism and functional properties of the cell.

TABLE 2. CONT'D.

Structure	Brief biochemical and functional characteristics	Particular sensitivity	Possible consequences
Mitochondria	Oxidizing enzymes, enzymes of the tricarbonic acid cycle, phosphorylization, etc., DNA, RNA, lipoproteids, proteins. Basic "energy status of cell".	Hypoxia; apparently react to all extreme stimuli.	Increase or decrease in energy resources and activity of the cell.
Lysosomes	Lipoproteids, acid proteolytic enzymes ("catepsins"), acid phosphotase, esterase. Principal role: digestion of absorbed particles and bacteria. Participation and processes of pino- and phagocytosis.	To the action of factors that disturb the permeability of the membranes. To free radicals, radiant energy, excess vitamin A, papaine, etc.; to vitamin E avitaminosis, hypoxia, endotoxins, etc.	Atrophy of cells, death, development of necrotic processes, involution, autolysis. Change in the protective properties of the cell.
Plasmatic membrane on the cell (plasma lemma)	Lipoproteids. Mucopolysaccharides. Basic functions: retention of the internal environment of the cell, selective absorption and excretion, phagocytosis, pinocytosis. Participation in the mechanism of the Na--pump, in the processes of aggregation of cells.	To surfactants. To snake venom, viruses, hypoxia, the action of free radicals.	To surfactants. To snake venom, viruses, hypoxia, the action of free radicals. In addition, disruption of various forms of nutrition of the cells, sodium--potassium balance, water content, specific functions of the cell. Death of cell.

The significance of the endoplasmatic reticulum is governed primarily by the detoxification processes in the form of so-called protective synthesis. They are largely dependent upon protein formation.

The constant intake of unsaturated fatty acids from the fat deposits in the liver may increase under various harmful influences on the organism. Usually the continuous secretion of triglycerides, culminating in the form of lipoproteids formed in the endoplasmatic reticulum, balances the lipid composition of the liver. However, the loss of the ability of the liver to synthesize protein disturbs the process of formation of lipoproteids and the entry into the blood, leading to adiposis of the liver. Insufficient synthesis of lipoproteids causes a disruption of the state of lipoproteid membranes upon which the permeability of various cell cultures depends. In addition to adiposis, necroses may develop in the liver. The reasons for the development of necroses in the liver are not clear. /22

Hence, damage to the cell may take various forms. It may depend not only on the condtiion of the nucleus but on the status of other structures in the cell as well. For example, to give some idea of the possible consequences that arise in the cytoplasm of the liver cells, let us look at the diagram compiled by Rees (Figure 3). The diagram shows the effect of free radicals and lipid peroxides formed in the organism under the influence of radiation, intoxication and other pathogenic factors on the cell organelles.

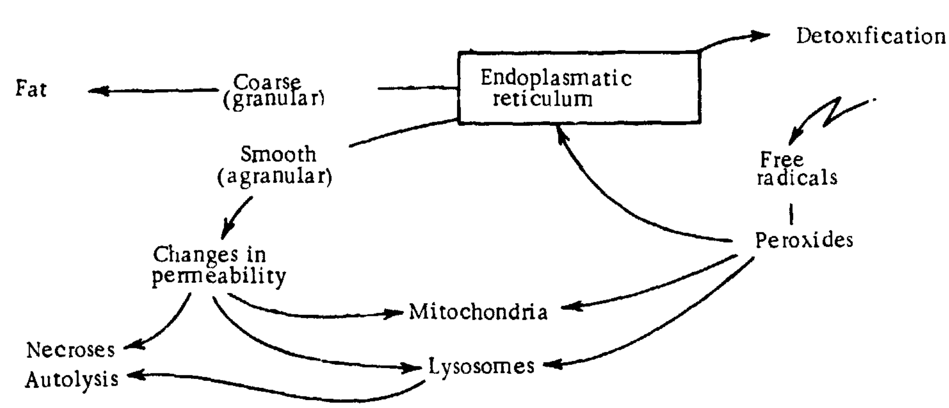


Figure 3. Influence of Pathogenic Factors on the Cytoplasmatic Structures of the Cell.

The biochemical basis for the processes described above is very complex and still insufficiently understood. We can merely state in passing that ATP is the necessary energetic component of all biosynthetic protective reactions of the cell. These include enzymes that participate in the restoration of the structures of DNA, RNA-polymerase, processes of oxidation and reduction of NAD and NADP of the flavoproteins, cytochromes, etc. When these substances are involved, the processes of reduction of harmful tissue may occur. When total reduction takes place, regeneration starts. If reduction takes place partially due to the formation of fibrous and scar tissue, we can speak of reparative or incomplete restoration.

Change in the Blood System and the Infection of the Organism

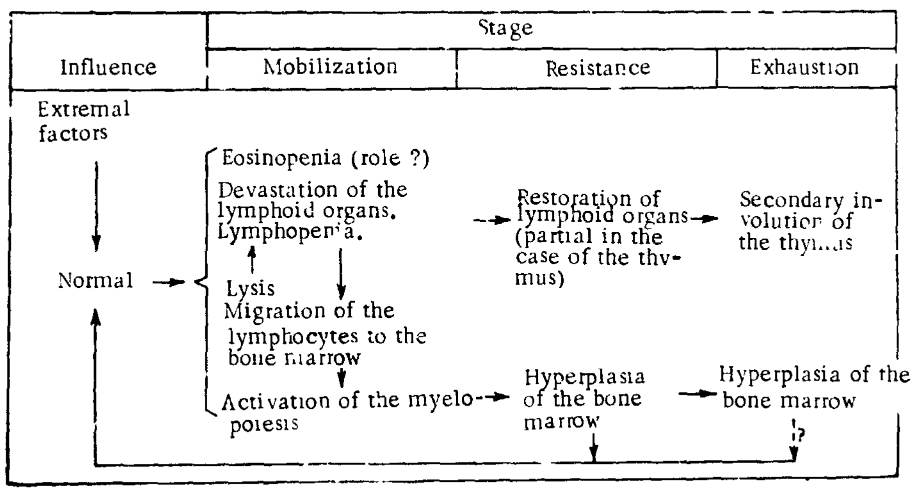
Animals and man are constantly exposed to the harmful acti microbes and viruses. However, as a result of evolutionary accomodation, the organism has worked out various mechanisms of protection, which may be conditionally divived into two periods as far as the time of their action is concerned: the initial period of "mute" struggle and the later period of "active reactions".

In the initial period, those properties of the blood which can be classified with the nonspecific factors of resistance to infection are of primary importance. These include proteins (histones and protamines), which localize and inactivate the action of living agents; natural antibodies; complement — serum protein, which splits the antigen-antibody complex by cytolytic action; properdine — serum euglobulin, which, in combination with complement and magnesium ions, possesses antibacterial and antivirusal properties; interseron and other antivirusal and bactericidal substances. The mechanisms of nonspecific protection include the process of capture of the microbes by the cells of the reticuloendothelial system.

While there is no destruction of the invasion in the initial period, a second period develops involving a struggle with the agents. This includes a change in circulation and composition of blood, development of inflammation, production of specific antibodies, activation of the reticuloendothelial system and other still more pronounced local and general reactions on the part of the organism. The blood plays an important role in these processes, particularly under conditions of extremal influences. Therefore, let us discuss briefly the /23
changes that occur in the blood composition and in hemopoiesis under stress reactions.

By using various extreme influences — stimulation with electric current, immobilization, bleeding, etc., we established a definite sequence for the changes in the blood which are represented schematically in Table 3 (P. D Gorizontov).

TABLE 3. CHANGES IN THE BLOOD SYSTEM



The most noticeable aspect of these changes is the development of temporary hyperplasia of the bone marrow. We feel that the increase in the myeloid tissue has a significant influence on the increase in nonspecific resistance of the organism, not only with respect to infection.

As experiments have shown, less intensive stressors (for example, daily administration of small amounts of physiological solution to rats) do not produce temporary hyperplasia of the bone marrow. However, judging by the change in the weight of the adrenals and the atrophy of the thymic-lymphatic system, the stress reaction may develop in response to even "weak" stimuli.

It is interesting to note that a decrease in the number of cells in the lymphoid organs (thymus, spleen) depends not only on the destruction of the lymphocytes, as was formerly thought, but also on the migration of lymphoid cells into various organs, particularly into the bone marrow. As was pointed out earlier, the lymphocytes which break down constitute a source of plastic material for synthesis of DNA, proteins and carbohydrates. The lymphoid cells which have migrated into the bone marrow play an important role in the processes of activation of myelo- and erythropoiesis. Some lymphoid cells are similar to trunk cells, and apparently serve as a source for the formation of the red and white types of bone marrow.

Special studies conducted by a number of investigators have shown that the sympathetic nervous system stimulates myopoiesis and has an effect on the migration of lymphocytes. Without the hormones from the adrenal cortex, there is no activation of myelopoiesis (P. D. Gorizontov, O. I. Belousova et al.).

Hence, judging by the blood system, the reactions which develop depend on /24
both the sympathetic nervous system and the corticosteroids. The biological significance of the changes in the cell composition of the blood is determined by its protective role. In this respect the blood granulocytes not only participate directly in the processes of phagocytosis, but also have the ability to affect cells which have undergone phagocytosis in the reticuloendothelial system. It is a fact that the capture of microbes is not a matter of indifference as far as their digestion and destruction is concerned.

If microbes are introduced into the blood, purification (clearance) of the blood to remove the microbes is accomplished, according to Rodgers, in three phases. In the first phase, which lasts a maximum of 90 minutes, there is a rapid decrease in the number of microbes. This process is independent of the state of the animal and the number of microbes introduced, inasmuch as the absorptive function of the blood cells and the reticuloendothelial system is extremely high. However, the intensity of the primary phase of blood clearance may change as a function of the type of agent introduced into the blood and the existence of antibodies in the blood. In the second phase, which lasts from 4 hours to several days, the number of microbes circulating in the blood may be insignificant. The microbes may even completely disappear from the blood, but this does not mean that the infection has been eliminated. The third phase, lasting from 6 hours to several days, is critical. In this third phase, either recovery will take place or the number of microbes will increase and bacteremia will develop, with all of the clinic[illegible] symptoms of sepsis (Figure 4).

What causes this phase pattern? As approp[illegible] studies have shown, the fate of the microbes not only depends on th[illegible]ion by the cells of the reticuloendothelial system but also on [illegible] the cells to destroy the microbes. The microbes that are absorbed sometimes do not die and even begin to multiply inside the cells of the reticuloendothelial system, spreading throughout the organism (third phase). This depends on the fact that the process of lysis (digestion) of the microbes is very labile. It can be disturbed by very diverse unfavorable factors that act on the organism (hunger, intoxication, trauma, /25 irradiation, etc.). To illustrate this viewpoint, let us examine the curve showing the content of Friedlander bacilli in the livers of mice that were fed or starved (Figure 5), taken from the work by Rodgers. We can see from the curve that during the first phase of clearance the microbe content in the livers of the mice that were starved and those that were fed (the controls) is the same. In the third phase, the starving mice begin to show a sharp increase in the number of bacteria in the liver, and the animals perish.

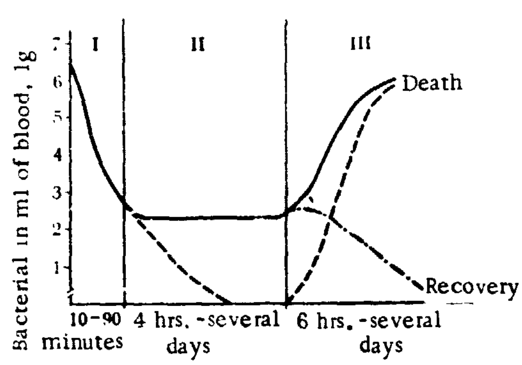


Figure 4. Diagram of Purification (Clearance) of the Blood Following internal Administration of Live Bacteria. I, II, III, Phase of Purification.

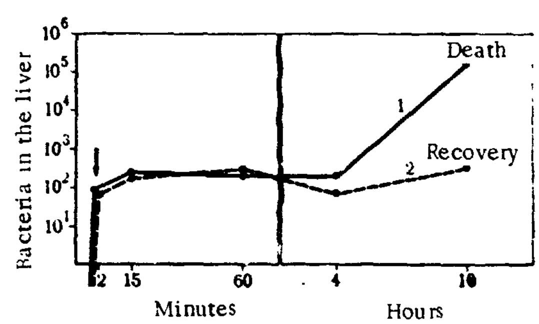


Figure 5. Change in the Number of Living Bacteria in the Livers of Mice That Were Fed (2) and Starved (1) Following Intravenous Injection of Friedlander Bacilli.

It has been established that the viability of phagocytized microbes also depends upon the level of the granulocytes in the peripheral blood (Smith, Nelson). In experiments involving irradiation of animals, it has even been possible to demonstrate the existence of a quantitative correlation. Thus, for example, when the number of leucocytes in the peripheral blood decreases by a factor of 2, the bactericidal properties of the macrophages decrease by a factor of 8. When the number of leucocytes in the peripheral blood drops below 1,000 mm, the number of intracellular microbes does not decrease; they do not die, and even multiply in the cells.

It has been suggested that the granulocytes, which are sometimes referred to as mobile sacs with lysosomes, evidently enrich the cells of the reticuloendothelial system with enzymes required for the hydrolytic decomposition of the microbes. For reasons that are not completely clear, a shortage of leucocytes is accompanied by a decrease in their ability to move rapidly and to collect precisely at the focus of the infection. Therefore significant leucopenia, caused by certain factors, is always accompanied by autoinfection of the organism. In these cases it is necessary to use antibiotics. Let us recall that during the stage of exhaustion hypoplasia of the bone marrow develops and the number of leucocytes in the peripheral blood gradually falls. This establishes a relationshop between the effect of the extreme stimuli, the change in the blood composition and the possibility of the spread of infection. The infection of the organism under conditions in which it is exposed to extreme influences may also be promoted by other factors in the form of a disruption of the intactness of integuments, reduction of bactericidal properties of the blood, etc.

Due to the lack of space, we shall not deal with problems of immunity, inflammation, fever and other protective reactions of the organism.

It has been established in experiments that when various organs are damaged (liver, kidneys, intestine), substances appear in the blood that stimulate the processes of cellular regeneration in precisely those tissues which have been damaged. As experiments have shown, the principal means by which the humoral factors which stimulate regeneration are developed consists of the lymphoid cells (A. G. Babayeva, N. A. Kraskina, L. D. Liozner, 1969).

Increasing the nonspecific resistance, caused artificially, for example by daily traumatizing of rats in a rotating drum, causes the appearance in the blood of humoral factors that increase the resistance of the organism. Injection of blood taken from resistant animals increases resistance in animals not previously exposed. It was further established that the reticuloendothelial system is the site where the humoral factors of resistance are developed. Blockage of the reticuloendothelial system by administration of colloidal iron eliminated increased resistance (Reichard, 1964). However, the function of the macrophages of the reticuloendothelial system in the development of specific and nonspecific forms of protection, according to the studies of R. V. Petrov, depends upon the activity of the lymphocytes and the trunk hemopoetic cells.

These materials provide a basis for discussing the functional interaction of the blood system and the reticuloendothelial system in the changes of the nonspecific resistance of the organism.

Brief Characterization of Several Problems With Functions of the Organism /26

Let us examine several examples of disruptions of functions which can be of great significance to the outcomes of damage under the influence of extremal factors.

We know that serious consequences can arise from hemorrhage. However, regardless of the disruption of the intactness of even large blood vessels, all the blood is never lost. The amount of blood remaining in the vessels is a function of a number of factors. Table 4 lists the principal factors which cause blood loss and the mechanisms that prevent hemorrhaging.

TABLE 4. PRINCIPAL FACTORS INFLUENCING THE DEVELOPMENT OF HEMORRHAGE AND THE MECHANISMS THAT PROMOTE RETENTION OF A PORTION OF THE CIRCULATING BLOOD

Influence on Intensity of Blood Loss	Factors Promoting Retention of Circulating Blood
Degree of disturbance of intactness of vessels, their size and blood supply to the tissues.	Constriction of vessels.
Reduction of functional status of coagulatory system of the blood.	Rate of formation of hemostatic thrombus and blood clots.
Thrombocytopenia, disruption of adhesion, aggregation and viscid metamorphosis of thrombocytes.	Primary hemostasis, formation of blood thrombus, its hardening.
Changes in connective tissue.	Intactness of basal membrane and retention of collagenic fibers in the perivascular space.
Increase in activity of fibrinolysis of the blood and tissue.	Prevention of fibrinolysis and fibrinogenolysis.
Insufficiency of vitamins K, C and P.	Increase in the ability of the blood to coagulate and the resistance of the vascular wall, decreased permeability.
Disruption of the liver function.	Synthesis of fibrinogen and other factors involved in blood coagulation.

TABLE 4. CONT'D.

Influence on Intensity of Blood Loss	Factors Promoting Retention of Circulating Blood
Decrease in the composition of cells of the erythro- and myeloid series.	Penetration of formed elements of the blood from the blood deposits — spleen, bone marrow.
Decrease in the functional activity of the kidneys.	Retention of the volume of circulating blood through retention of sodium and water.

A shortage of vitamin C promotes the development of hemorrhages, exactly as the disruption of the functional state of the connective tissues does. In fact, the capillary endothelium is surrounded on the outside by a layer of substance (connective tissue) called the basal membrane. Therefore, the changes in the connective tissue properties lead to increased capillary permeability (for example, in some forms of syphilis, senile purpura and other diseases). An important role in the formation of the basal membrane is played by vitamin C. As we know, hemorrhages develop in C hypovitaminosis (scurvy).

Endothelial cells are connected externally with one another by a so-called cement (calcium proteinate) which is produced by the endothelial cells. The disruption of the intactness of the cement and an increase in intracellular space influences the permeability of the capillary cells, promoting the develop- /27 ment of hemorrhages.

Thrombocytopenia from any cause may be a basis for the development of hemorrhages, caused by the multilateral role of the thrombocytes. The ability of the thrombocytes to "stick" to the damaged endothelium and collagen (adhesiveness), their aggregation under the influence of thrombin, ADP, serotonin, etc., promotes the formation of a primary thrombocytic thrombus containing threads of fibrin, the activation of the blood coagulation system and the formation of a blood clot, which ensures reliable hemostasis. The interaction of the thrombocytes with collagen occurs without the participation of blood coagulation processes.

An increase in the fibrinolytic activity of the blood and increased tissue fibrinolysis cause disruption of the hemostatic thrombus and blood clot, resulting in the development of secondary hemorrhages. This is promoted by the disruption of the process of formation of insoluble fibrin which occurs, for example, in the case of inherited insufficiency of the fibrin-stabilizing factor (factor XIII). The products of fibrinolysis and fibrinogenolysis reduce the ability of the blood to coagulate, disturb the process of polymerization of the fibrin, and prevent adhesion and aggregation of thrombocytes. Thrombocytopenia and disruption of the blood supply to organs and tissues promote increased fibrinolysis.

In addition, the thrombocytes give off serotonin, which causes vasoconstriction and a decrease in the plethora of the tissues, which also limits hemorrhaging. Serotonin is formed primarily in the enterochromaffinic cells of the intestine, where it is captured by the thrombocytes. The serotonin circulting in the blood is destroyed in the liver. The role of the kidneys will be discussed below.

The problems of hemophilia and blood coagulation are very extensive. They constitute the subject of special areas of hematology, and so, limiting the material in the table we can move on to the question of disruption of peripheral circulation, since it is on this that the activity of any tissue or organ depends.

Circulation is conditionally divided into central and peripheral varieties. Central circulation is mainly under the influence of the nervous system. The problem of the regulation of the peripheral blood circulation has largely still not been solved. In explaining the reasons for local changes in circulation, two trends have developed: myogenic and metabolic. According to the former, the primary significance attaches to the influence of the intervasculer pressure on the smooth musculature of the vessels. According to the latter, regulation of blood flow takes place under the influence of locally active metabolites. Without going into an evaluation of the details, let us simply recall that the changes in peripheral circulation are governed primarily by the sizes of the lumina of the arterioles. In the norm, the constantly present tone of the fibers of the sympathetic nervous system innervating the arterioles is accompanied by the excretion of noradrenaline. Noradrenaline causes a slight pressure on the smooth musculature of the walls of the arterioles. Therefore, a weakening /28 of the tone of the sympathetic nervous system causes a dilation of the vessels and, on the other hand, an increase in tone produces a still greater constriction of the arterioles. The only exception is constituted by the coronary vessels of the heart and brain.

The effect of adrenaline on the vessels has a dual nature. Wherever α-receptors are predominant in the smooth musculature, a vasoconstrictory effect develops; when β-receptors predominate, vasodilatory effects can be seen.

Peripheral circulation is a function of the number of functioning capillaries. Their activity is determined by the presence of precapillary sphincters. The sphuncters are affected by substances circularing in the blood or formed locally, which have a vasomotor effect (Figure 6).

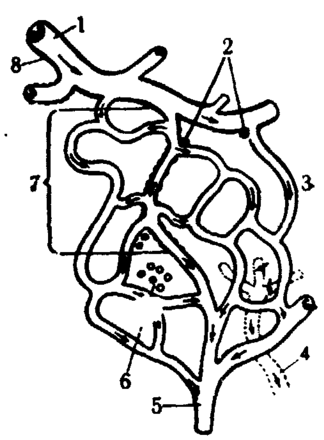


Figure 6. Diagram of Peripheral Blood Circulation in the Mesentry. 1, Neurogenic control, pressor substance of the blood; 2, sphincters of the precapillaries; 3, circulating pressor and trophic substances, catabolites, vascular-active substances, formed locally; 4, lymphatic vessels; 5, venules; 6, adipose cells, macrophages, eosinophils; 7, precapillaries; 8, arterioles.

Insufficiency of peripheral circulation, caused by factors of all sorts (thrombi, emboli, shock, collapse, etc.), causes a number of local and general changes, listed in Table 5.

The corticosteroids, thyroid gland hormone, and renal stimulants increase vascular reactivity.

If we take into account the various consequences of disruption of peripheral circulation, we must also keep in mind the functional significance of the organ and its sensitivity to the blood supply. Inadequate blood supply to the brain or heart muscle may result in the death of the organism. Insufficient blood supply to the skin for a long period of time is possible without any particular consequences for the ischematized tissue. Regulation of cutaneous circulation is largely dependent on thermoregulatory processes and not on the needs of the tissue itself.

TABLE 5. INFLUENCE OF VARIOUS FACTORS ON PERIPHERAL CIRCULATION

Factors Influencing Local Circulation	Consequences of Circulatory Insufficiency
The following dilate the vessels and increase the influx of blood: Histamine Organic acids (galactic, etc.) Kinins Heparin Ferritin	Accumulation of tissue catabolites promotes the retention of dilation of capillaries and an increase in permeability. Against the background of increased permeability, edema and tissue hypoxia may develop.
The following constrict the vessels and reduce circulation Noradrenaline Adrenaline Serotonin and other pressor amines Angiotensin	A decrease in local circulation may lead to hypoxia of organs and tissues. Hypoxia of the liver causes accumulation of toxins, excretion of ferritin, decreased inactivation of aldosterone. Hypoxia of the brain leads to loss of consciousness and the development of a syncopal condition, hypoxia of the heart leads to a weakening of cardiac activity. In the case of systemic (general) disruption of circulation, excretion of pressor substances may lead to functional failure of the kidneys and development of oliguria. Atrophy. Necrosis.

Under the influence of extremal factors, a general disruption of peripheral /29 circulation frequently occurs. It is characteristic of such states as shock and collapse.

Defining the concepts of shock and collapse is rather difficult. In shock, the critical role is played by disruption of central regulation of peripheral blood circulation. Collapse constitutes acute vascular insufficiency as a result of damage to the vascular walls and disruption of their reactivity. Collapse is characterized by a sharp drop in arterial and venous pressure, increased vascular permeability, development of hypoxemia and hypoxia. Collapse frequently arises instantaneously, with symptoms of general weakness, sometimes with loss of consciousness. Intoxication is the most frequent cause of development of collapse (see Chapter 9).

With general disruption of the peripheral circulation, one could expect development of edema due to increased permeability of the capillaries, a decrease in activation of aldosterone and suspension of sodium excretion from the organism. However, edema does not develop, because the plethora of the capillaries in general disruption of the peripheral circulation (for example, in shock) is a symptom of stasis rather than plethora.

Edema is a disruption of water balance characterized by excessive accumulation of fluid in the tissues. As a rule, edema arises as a result of the joint effect of a number of factors (Ya. A. Lazaris, I. A. Serebrovskaya, 1968). According to the data of Black and Wagner (1964), the conditions leading to the development of edema can be listed as in Table 6.

TABLE 6. FACTORS PROMOTING FORMATION OF EDEMA

Factor	Consequences
Increased blood volume due to sodium retention or decreased diuresis.	Capillary hyperemia.
Increase in capillary permeability: Toxic Hypoxic Allergic	Increased loss of protein in the interstitial spaces.
Hypoproteinemia: Metabolic disease, exhaustion	Decrease in oncotic pressure (decrease in resorption of fluid).
Blockage of veins or lymph vessels: by thrombi, by external pressure, due to infectious damage to the vessels	Insufficient removal of interstitial fluid.
Reduction of tissue elasticity: due to dietary deficiencies genetic defects	Increased formation or reduced elimination of interstitial fluid

Under extremal influences edema caused by insufficient cardiac activity developed. A number of changes then occur. /30

Insufficient cardiac activity causes decreased renal glomerular filtration, increased sodium resorption, and stimulation of the baroreceptors. This causes increased antidiuretic hormone excretion by the posterior lobe of the pituitary (ADH). The effect of ADH is characterized by increased water resorption in the distal renal tubules. The increased circulating blood results in an increase in the number of functioning capillaries. This is accompanied by increased fluid perfusion into the intervascular spaces, its accumulation in the tissues and the development of edema. Under such conditions, blood flow decreases and the hypoxia develops, in turn promoting increased capillary plethora. The hypoxic changes in the liver reduce its ability to inactivate aldosterone (adrenocortical hormone which promotes sodium retention in the organism). Aldosterone excretion occurs primarily under the influence of the pressor action of angiotensin, formed from α_2-globulins of blood plasma under the influence of renin excreted by the renal juxtaglomerular cells.

Hypoxia which develops in cardiac insufficiency promotes the excretion of vasodepressor substances (ferritin) from the liver into the peripheral blood, constituting an additional stimulation of ADH secretion.

Thus, on the basis of fluid retention and development of capillary plethora, a number of vicious circles are created which increase the work of the heart and the degree of cardiac insufficiency.

The changes described above not only constitute the disease, but may also play the roles of physiclogical measures against the disease. Thus, when the circulating blood volume decreases sharply (for example, due to extensive hemorrhaging), the rapid initiation of the mechanisms which change the function of the kidneys counteracts the decrease in the circulating blood volume, retaining water and promoting the access of tissue fluids into the vascular bed. The processes which occur at this time are shown schematically in Figure 7.

Let us mention in passing that restoration of arterial pressure during rapid hemorrhaging is a function not only of the circulating blood volume but also the change in the rhythm of cardiac activity and spasms of the vessels in the internal organs and cutaneous coverings. The initiation of these mechanisms is ensured by the action of the nervous system, especially by the increase in the tone of the sympathetic nervous system and the excretion of catecholamines into the blood. The reactions of the organism to hypoxia due to blood loss are discussed in more detail in Chapter 7.

In extremal states, a significant danger may be posed by pulmonary edema. This development is associated with a disruption of the lesser circulation. However, one must keep in mind that the development of pulmonary edema may depend upon a direct harmful effect of toxic substances on the alveolar cells (see Chapter 12) or even upon damage to certain parts of the central nervous system (hypothalamus). In turn, the preliminary effect of nonspecific stimuli on the central nervous system may prevent the development of pulmonary edema (G. I. Kositskiy, M. M. Smirnov). A drop in venous pressure, caused by blood loss, is one active measure against pulmonary edema.

Renal pathology can arise under diverse extremal states: hypoxia, shock, burn disease, blood loss or intoxication (see Chapters 2, 3, 4, 8 and 9). In this connection, it is necessary to devote some attention to their significance in the regulation and the disruptions of the functions of the organism.

In the kidney, as in any other organ, the activities of the various parts are specialized. They depend on the function of many other organs: cardiovascular system, endocrine glands (hypophysis, adrenals, parathyroid gland), liver and so forth.

In addition, the effectiveness of renal function is determined by the processes of excretion of urine which continue even beyond the kidney (the state of permeability of the urinary tract).

Let us examine the complicated table that characterizes the basic functions of the kidneys and the most important consequences of their disturbance (Table 7).

It is clear from Table 7 that serious consequences will arise from a disruption of the ability of the kidneys to excrete the end products of nitrogen metabolism. This causes the development of uremia.

Depending on the seriousness of the disease, the development of azotemia (and subsequently uremia) may occur at any location of damage in the kidney tissue. If good concentrating ability of the kidneys has been retained, a small amount of urine excreted from the organism will take with it a significant amount of nitrogenous substances. With a large amount of urine and a low specific gravity, the nitrogen-excreting function of the kidneys may also be adequate. Therefore, even sharp quantitative changes in diuresis will not necessarily be indicative of the possibility of the element of azotemia, not to mention uremia.

TABLE 7. PRINCIPAL FUNCTIONS OF THE KIDNEYS AND THE CHARACTERISTICS OF THEIR DISRUPTION

Principal Functions	Localization of Functions	Factors Influencing Function	Most Important Consequences of Disruption of Function
Excretion of water, salts and glucose. Participation in the regulation of water balance, sodium balance (Na-pump).	In the glomeruli.	Blood supply and blood pressure. Osmotic and oncotic pressure of the blood. Permeability of the endothelium of the glomerular vessels.	Quantitative changes in diuresis. Proteinuria and hematuria. Hypertonic state.
Active resorption (up to 80%) of sodium, chloride (up to 100%), potassium, glucose (with levels up to 160 mg% in the blood). Passive absorption of water.	Proximal tubules.	Under the influence of cytotoxic substances, heavy metals, etc., there is a decrease in the size of the lumen of the tubules due to swelling and necrosis of the epithelium ("tubular blockage").	Acute anuria. Disruption of resorption of water and salts. Proteinuria. Sodium retention.
Active resorption of Na with metabolic excretion of K.	Ascending portion of the loop of Henle, distal tubules.	Aldosterone insufficiency.	Sodium loss.
		Excess aldosterone.	Potassium loss.
Absorption of water from the tubules and development of a con concentration capacity by the kidneys.	Ascending portion of the loop of Henle, distal tubules.	High ADH level.	Oliguria, edema.
		ADH insufficiency.	Disruption of osmotic regulation. Polyuria.
Participation in the regulation of acid-alkaline balance. Formation of hydrogen ions over the entire area of the convoluted tubules.	Distal tubules.		Disruption of acid-base balance.

TABLE 7. CONT'D.

Principal Functions	Localization of Functions	Factors Influencing Function	Most Important Consequences of Disruption of Function
Partial excretion of them.			
Synthesi^ of NH_3 as the result of splitting of glutamine and α-amino acids by glutaminase and α-aminooxidase. Combination of H^+ with ammonia, formation of ammonia ions. Reabsorption of bicarbonate into the plasma.		Excretion of alkali, parathyroid tetany, etc.	Alkalosis possible.
Substitution of Na^+ for H^+ in the bicarbonate, phosphates. Substitution of Na^+ in the balance with chlorides.	Distal tubules.	Insufficiency of carbonic anhydrase (for example, under the influence of diuretics)	Acidosis and sodium loss.
Participation in the regulation of phosphorus and calcium metabolism (excretion of phosphates and calcium).	Renal tubules.	Hyperphosphatemia of any etiology causes increased secretory activity of the parathyroid glands, which affect not only the excretion of phosphates and Ca but also the mobilization of Ca from the bones.	Phosphaturia, hypophosphatemia. Increased Ca excretion. Mobilization of Ca from the bones (osteomalation). Defective formation of bones (nitrogen osteodystrophy). "Renal rickets" (resistant to the effects of vitamin D).
Passive excretion of products of nitrogen metabolism. Active secretion of a small quantity of creatinine.	All parts of the nephron.	Obliteration of the glomuralize; decrease in the filtration pressure (significant hypotonia, shock, collapse, etc.); damage to the epithelium and "tubular blockage"; anuria or acute oliguria from other causes; disruption of the permeability of the urinary tract.	Azotemia. Uremia. Symptoms in the brain: headaches, spasms, coma. Fibrinous changes in the serous coverings. Ulceration of mucous membranes of the stomach and intestines. Disturbance of the function of the heart and regulation of blood pressure.

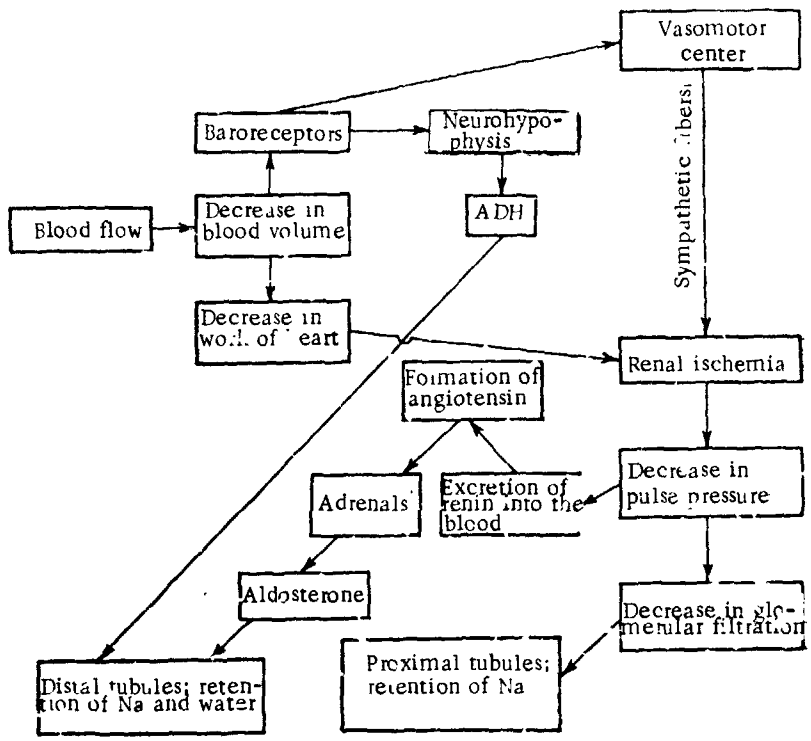
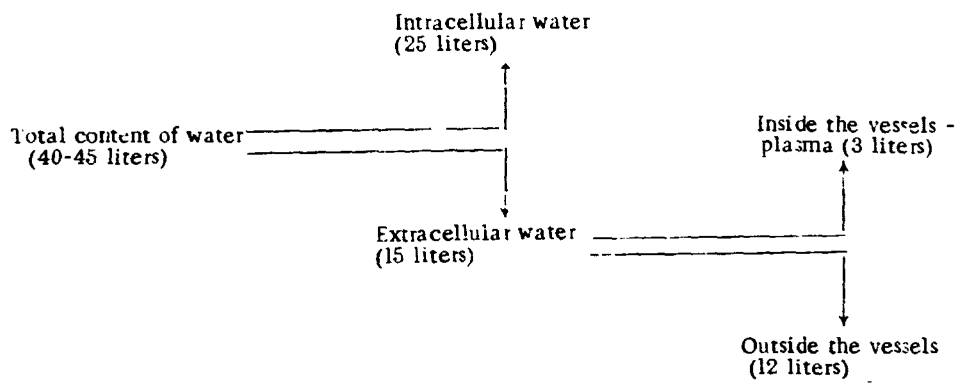


Figure 7. Diagram of the Inclusion of the Kidney Reaction in Adequate Blood Flow.

Damage to tubular epithelium occurs for various reasons, including the entry into the tubules of substances which are difficult to excrete, in the form of myoglobin (lower nephrosis in the reproductive syndrome), bile (cholemic nephrosis), etc. Tubular blockage may have serious consequences. However, these consequences may be of a temporary nature, since the regenerative capacity of the tubules is very high. Therefore, measures must be aimed at correction of the problems that develop in anticipation of a comparatively rapid regeneration of the epithelial tissue of the tubules and the recovery of their function.

The kidneys play an important role in the regulation of the aqueous composition. The total amount of water in an adult man is approximately equal to 2/3 of the weight of the organism. Redistribution of water among different areas is represented approximately by the following figures:



As we mentioned earlier, the kidneys influence the circulating blood (plasma) volume by changing the level of diuresis and sodium retention under the influence of two hormones: ADH and aldosterone. Note that the functional antagonist of ADH consists of the glucocorticoids, which may decrease edema and eliminate the undesirable consequences of excessive ADH secretion, for example, in cardiac insufficiency. /34

The functional antagonist of aldosterone is spironolactone.

The kidneys regulate salt composition. Let us recall that the salt composition is important in the maintenance of the osmotic level of the internal environment of the organism; in addition, the concentrations of various ions affect the properties and behavior of various excitable membranes (nerve, muscle cells, etc.) and the effect of the majority of intracellular enzymes.

The electrolytic composition of the cellular and extracellular fluids differ. In the cells, the principal cations are K and Mg; the anions are phosphates and proteins. The principal cation outside the cells is Na, while the principal anions are chlorides and bicarbonates.

Intracellular K bears relationships to protoplasm. Therefore, an increase in potassium in the extracellular medium and in the urine can serve as a symptom of cellular breakdown.

Participation of the kidneys in the regulation of phosphorus and calcium metabolism must be taken into account in conjunction with problems of space medicine, since it has been demonstrated that it is possible for cosmonauts to develop disturbances of calcium metabolism under certain conditions (see Chapter 10).

In concluding this brief and far from complete survey, we would like to suggest that the material in this chapter characterizes the role of the basic features of resistance and protection. At the same time, we have tried to show the significance of some of the general disturbances of functions on the cellular, systemic and organismal levels, which frequently arise under the influence of extremal factors.

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